Attorney's Docket No.: 00786-429001
Client's Ref. No.: MGH-1424.0

**OFFICIAL COMMUNICATION**

**FACSIMILE**

**FOR THE PERSONAL ATTENTION OF:**

**EXAMINER ANA M. FORTUNA**

**GROUP 1723 FAX NO: (703) 872-9310**

**Number of pages including this page** 5

Applicant : William Lee et al.
Serial No. : 09/728,882
Filed : December 1, 2000

Art Unit : 1723
Examiner : Ana M. Fortuna

FACSIMILE COMMUNICATION

Title : METHODS FOR REMOVAL, PURIFICATION, AND CONCENTRATION OF VIRUSES, AND METHODS OF THERAPY BASED THEREUPON

Commissioner for Patents
Washington, D.C. 20231

Examiner Fortuna:

As we discussed, I have enclosed two (2) references regarding the use of the word pyrogen. Please call me at (617) 542-5070 to discuss possible allowance of this case.

Respectfully submitted,

Date: November 18, 2002

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Reg. No. 32,983

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20542164.doc

14TH EDITION

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VOLUME 1

# Harrison's PRINCIPLES of INTERNAL MEDICINE

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defining the 99th percentile for healthy individuals. Given these criteria, *an A.M. temperature of greater than 37.2°C (98.9°F) or a P.M. temperature of greater than 37.7°C (99.9°F) would define a fever.* Rectal temperatures are generally 0.6°C (1°F) higher. Lower esophageal temperatures closely reflect core temperature. The temperature of a freshly passed urine specimen is close to rectal values. The normal 24-h circadian temperature rhythm is associated with temperatures varying typically by 0.5°C (0.9°F) but occasionally by as much as 1.8°C between the A.M. nadir and the P.M. peak. This morning-low and evening-high pattern is usually preserved in febrile diseases but not in hyperthermia. In menstruating women, the A.M. temperature is generally lower in the 2 weeks prior to ovulation, rising by about 0.6°C (1°F) with ovulation and remaining at that level until menses occur. In addition, there may be a seasonal variation in body temperature. Finally, such physiologic factors as postprandial state, pregnancy, endocrine alterations, and age may affect baseline temperatures.

**PYROGENS** Substances that cause fever are called *pyrogens* and may be either exogenous or endogenous. *Exogenous pyrogens* come from outside the host, whereas endogenous pyrogens are produced by the host, generally in response to initiating stimuli that are usually triggered by infection or inflammation. The majority of exogenous pyrogens are microorganisms, their products, or toxins. The best-characterized type of exogenous pyrogen consists of a heterogeneous group of molecules that is common to all gram-negative bacteria and is referred to as *endotoxin* (lipopolysaccharide, LPS). LPS, which is found in the outer membrane of all gram-negative bacteria, comprises lipid A and a polysaccharide core linked to an O-polysaccharide side chain composed of repeating units of sugars that vary with the gram-negative organism. Gram-positive organisms also are sources of potent pyrogens. These include cell wall–derived lipoteichoic acid and peptidoglycans. Several exotoxins and enterotoxins produced by pathologic strains of streptococci and staphylococci act as bacterial superantigens—polyclonal T-lymphocyte activators that bind to the variable region of the T-cell receptor rather than in the antigen-binding pocket of the receptor. This binding leads to the activation of cells of many specificities, with resultant mediator release and tissue damage. These toxins are thought to contribute to both staphylococcal and streptococcal toxic shock. In vivo, as little as 1 ng of LPS/kg is capable of producing fever in humans; although there are no in vivo data for humans, gram-positive cell-wall constituents generally require a 2- to 3-log larger amount of material by weight to induce the production of endogenous pyrogens in vitro.

In general, exogenous pyrogens act primarily by inducing the formation of endogenous pyrogens through stimulation of the host's cells—usually monocytes and macrophages. However, the distinction between exogenous and endogenous pyrogens is sometimes blurred. For example, LPS may act directly on endothelial cells in the brain to generate fever, whereas many exogenous products result in the release of endogenous pyrogens, thereby causing fever. Such endogenous substances include antigen-antibody complexes with complement, complement cleavage products, steroid hormone metabolites, bile acids, and some cytokines.

*Endogenous pyrogens* are polypeptides produced by a variety of host cells, particularly monocytes/macrophages. Endogenous pyrogens, produced either systemically or locally, gain entrance to the circulation and produce fever at the level of the thermoregulatory center of the hypothalamus.

It was originally thought that there was a single endogenous pyrogen. The standard experimental model utilized injection of leukocyte supernatants or sera from febrile rabbits into normal rabbits. It was then realized that there are two leukocyte endogenous pyrogens: interleukin (IL) 1α and IL-1β. These two interleukins have a common molecular weight of approximately 17.5 kDa, have only 26 percent amino acid sequence homology, and bind to the same receptors. Originally thought to be produced only by phagocytic cells, IL-1α or IL-1β is also produced by endothelial cells, B lymphocytes, natural killer cells, fibroblasts, smooth-muscle cells, keratinocytes, and glial cells. Because of the ubiquitous production of these and other interleukins, cell-derived inflammatory polypeptides, and growth-promoting peptides, the more general term *cytokine* has been adopted to refer to these substances. Cytokines are regulatory polypeptides produced by a large variety of nucleated cells. Specifically, cytokines are produced by monocytes/macrophages, lymphocytes, endothelial cells, hepatocytes, epithelial cells, keratinocytes, and fibroblasts as well as other cells. Cytokines typically act locally, initiating autocrine (self-stimulating) or paracrine (nearby-stimulating) effects. When found in the circulation, cytokines are usually present in picogram-per-milliliter concentrations.

The major fever-inducing cytokines appear to be IL-1α, IL-1β, tumor necrosis factor α (TNFα), interferon (IFN) α, and IL-6. When any of these cytokines is administered intravenously to humans, chills and fever develop within 1 h. IL-1α and -1β are the most pyrogenic, with temperatures of 39°C developing in response to doses of 1 to 10 ng/kg of body weight. Doses of 100 ng/kg have caused higher fevers and rigors. TNFα produces chills and a temperature of 39°C at somewhat higher doses (50 to 100 ng/kg). IL-6 is the least pyrogenic of these cytokines, producing a temperature of 39°C at 10 μg/kg. IFNα and IFNγ have been administered primarily by the subcutaneous route; therefore, chills and fever develop after 3 to 4 h. On a weight basis, the interferons are less potent than IL-1 or TNFα and similar to IL-6. Moreover, the degree of fever elicited decreases with repeated injections of interferon. Studies with genetically altered mice have revealed that IL-1 and TNFα cause fever by inducing IL-6 in the brain.

**HYPOTHALAMIC CONTROL OF TEMPERATURE** Body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals—one from peripheral nerves that reflect receptors for warmth and cold and the other from the temperature of the blood bathing the region. These two signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral environment, the metabolic rate of humans consistently produces more heat than is necessary to maintain the core body temperature at 37°C. Therefore, the hypothalamus controls temperature by mechanisms of heat loss.

Clusters of neurons in the preoptic/anterior hypothalamus are supplied by a rich and permeable vascular network with limited blood-brain barrier function. The specialized vascular network is called the *organum vasculosum laminae terminalis*. It is likely that the endothelial cells of this network release arachidonic acid metabolites when exposed to endogenous pyrogenic cytokines from the circulation. The arachidonic acid metabolites—mainly prostaglandin $E_2$ ($PGE_2$)—then presumably diffuse into the preoptic/anterior hypothalamic region and initiate fever. It is also possible that $PGE_2$ or other arachidonic acid products induce a second messenger such as cyclic AMP, which in turn raises the thermoregulatory set point. $PGE_2$ is the most potent of the fever-producing arachidonic acid derivatives when injected directly into the hypothalamus and is believed to mediate the rise in the thermoregulatory set point. With the new, higher "thermostatic setting," signals go to various efferent nerves, particularly those sympathetic fibers innervating the peripheral blood vessels, which in turn initiate vasoconstriction and promote heat conservation. The thermoregulatory center also sends signals to the cerebral cortex, initiating behavioral changes such as seeking a warm environment, putting on more clothes, and special posturing. With the shunting of blood from the periphery and these behavioral changes, the body temperature usually rises by 2 to 3°C; if the hypothalamus calls for more heat, shivering (involuntary muscle contraction) is triggered to increase heat production. The combination of heat conservation and increased heat production continues until the temperature of the blood bathing the anterior hypothalamic neurons matches the new "setting." At that point, the hypothalamus maintains the new febrile temperature (Fig. 17-1).

The hypothalamic set point is reset downward by the disappearance of stimulating pyrogenic cytokines or by the inhibition of local prostaglandin synthesis by cyclooxygenase inhibitors such as aspirin and ibuprofen. The reduction of fever by acetaminophen involves the

# McGraw-Hill Dictionary of Scientific and Technical Terms

## Fifth Edition

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cane sugar, and ferroelectric barium titanate. { ˌpīrōiˌlekˈtrik ˈkrist-əl }

**pyroelectricity** [SOLID STATE] The property of certain crystals to produce a state of electrical polarity by a change of temperature. { ˌpīrōˌiˌlekˈtris-əd-ē }

**pyrogallic acid** [ORG CHEM] $C_6H_3(OH)_3$ Lustrous, light-sensitive white crystals, melting at 133°C; soluble in alcohol, ether, and water; used for photography, dyes, drugs, medicines, and process engravings, and as an analytical reagent and protective colloid. Also known as pyrogallol. { ˌpīrōˈgal·ik ˈas-əd }

**pyrogallol** *See* pyrogallic acid. { ˌpīrōˈgaˌlōl }

**pyrogallolphthalein** *See* gallein. { ˌpīrōˌgal·ōˈthal·ē-ən }

**pyrogen** [BIOCHEM] A group of substances thought to be polysaccharides of microbial origin that produce an increase in body temperature when injected into humans and some animals. { ˈpīrəˌjən }

**pyrogenesis** [GEOL] The intrusion and extrusion of magma and its derivatives. { ˌpīrōˈjenrə-səs }

**pyrogenetic mineral** [MINERAL] An anhydrous mineral of an igneous rock, usually crystallized at high temperature in a magma containing relatively few volatile components. { ˌpīrō-jəˈned·ik ˈminrəl }

**pyrogenic distillation** [CHEM ENG] A cracking process that runs at high temperatures, high pressures, or both, resulting in greater yields of the light hydrocarbon components of gasoline. { ˌpīrōˈjen·ik ˌdist·əlˈā·shən }

**pyroligneous** [CHEM ENG] Referring to a substance obtained by the destructive distillation of wood. { ˌpīrōˈlig·nē·əs }

**pyroligneous acid** [ORG CHEM] An impure acetic acid derived from destructive distillation of wood or pine tar. Also known as pyracetic acid; wood vinegar. { ˌpīrōˈlig·nē·əs ˈas·əd }

**pyrolithic acid** *See* cyanuric acid. { ˌpīrōˈlith·ik ˈas·əd }

**pyrolusite** [MINERAL] $MnO_2$ An iron-black mineral that crystallizes in the tetragonal system and is the most important ore of manganese; hardness is 1–2 on Mohs scale, and specific gravity is 4.75. { ˌpīrəˈlūˌsīt }

**pyrolysate** [CHEM] Any product of pyrolysis. { pīˈrälˈəˌzāt }

**pyrolysis** [CHEM] The breaking apart of complex molecules into simpler units by the use of heat, as in the pyrolysis of heavy oil to make gasoline. { pəˈrälˈə-səs }

**pyromagma** [GEOL] A highly mobile lava, oversaturated with gases, that exists at shallower depths than hypomagma. { ˌpīrōˈmagmə }

**pyromania** [PSYCH] A monomania for acting or watching fires. { ˌpīrōˈmānēə }

**pyrometane** *See* brookite. { ˈpīrōˈmeˌlān }

**pyromellitic acid** [ORG CHEM] $C_6H_2(COOH)_4$ A white powder with a melting point of 257–265°C; used as an intermediate for polyesters and polyamides. Abbreviated PMA. { ˌpīrōməˈlid·ik ˈas·əd }

**pyromellitic dianhydride** [ORG CHEM] $C_6H_2(C_2O_3)_2$ A white powder with a melting point of 286°C; soluble in some organic solvents; used for curing epoxy resins. Abbreviated PMDA. { ˌpīrōməˈlid·ikˌdī·anˈhīˌdrīd }

**pyrometallurgy** [MET] High-temperature process metallurgy. { ˈpīrōˈmed·əlˌərjē }

**pyrometamorphism** [PETR] Contact metamorphism at temperatures near the melting points of the component minerals. { ˈpīrōˌmed·əˈmórˌfiz·əm }

**pyrometasomatism** [PETR] Forming of contact-metamorphic mineral deposits at high temperatures by emanations from the intrusive rock, involving replacement of the enclosing rock with the addition of materials. { ˈpīrōˌmed·əˈsō·məˌtiz·əm }

**pyrometer** [ENG] Any of a broad class of temperature-measuring devices; they were originally designed to measure high temperatures, but some are now used in any temperature range; includes radiation pyrometers, thermocouples, resistance pyrometers, and thermistors. { pīˈrām·əd·ər }

**pyrometric cone** *See* Seger cone. { ˈpīrəˈmeˌtrik ˈkōn }

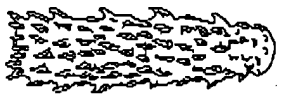
**pyrometry** [THERMO] The science and technology of measuring high temperatures. { pīˈrämˈə-trē }

**pyromorphite** [MINERAL] $Pb_5(PO_4)_3Cl$ A green, yellow, brown, gray, or white mineral of the apatite group, crystallizing in the hexagonal system; a minor ore of lead. Also known as green lead ore. { ˈpīrōˈmórˌfīt }

**pyromucic acid** *See* furoic acid. { ˈpīrōˈmyūˈsik ˈas·əd }

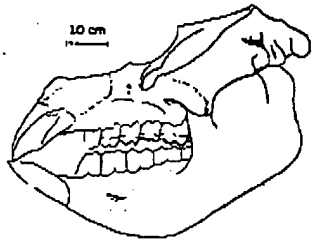
**pyron** [PHYS] A unit of area-density of power, equal to the

PYROSOMIDA



Colony of *Pyrosoma atlanticum*.

PYROTHERIA




Skull and jaw of *Pyrotherium sorondi*, an early Oligocene from South America.

area-density of p
tional table calori
-1 square centime
{ ˈpīˌrān }

**pyrone detector** cation occurs ben points. { ˈpīˌrōn

**pyrope** [MINERA garnet group char ring in basic and

**pyrophane** *See* fa

**pyrophanite** [M hedral mineral cc phous with ilmen

**pyrophobia** [PS bē-ə }

**pyrophoric alloy** produces a spark used for automat form that spontan atures. { ˈpī-rəˌf

**pyrophoric prop** of a liquid fuel an react when broug temperature. { ˈ

**pyrophosphatas** drolysis of esters phoric acid to fo sfə,tās }

**pyrophosphoric** ble, syrupy liqui make organic phc

**pyrophyllite** [M gray, or brown p occurs in a foliate granites, and meta { ˌpīrōˈfiˌlīt }

**pyroretinite** [MI coals of Aussig (U { ˌpīrōˈret·ənˌīt }

**pyroschist** [PET high carbon cont volatile hydrocarl

**pyrosin** *See* tetral

**pyrosmalite** [M less, pale-brown, of basic iron man

**Pyrosomida** [IN class Thaliacea ir nies and are often

**pyrosphere** [GE sphere, consistin { ˈpī-rəˌsfir }

**pyrostat** [ENG] ates a warning or A high-temperatu

**pyrostibite** *See* k

**pyrostilpnite** [M composed of silv crystal tufts; il rə'stilpˌnīt }

**pyrotechnic cod** various colors an smokes used for ground and air.

**pyrotechnic pist** cifically for proje tal }

**pyrotechnics** [I fireworks. [MAT and nonmilitary ] nation, or colorec consumed in the

**pyrotechnic sign** use to produce a transmitting infor

**Pyrotheria** [PAL itive, mastodonlil